September 2010

Primary Biliary Cirrhosis: Confirming Gene Involvement

New findings out of the laboratories of UHN's Drs. Katherine Siminovitch, Jenny Heathcote and Gideon Hirschfield confirm that certain genes involved in primary biliary cirrhosis (PBC)—the most common autoimmune liver disease—have genetic overlap, or involvement, in other autoimmune diseases commonly found in patients with PBC and their families.

Building upon a previous study in 2009 and published in the *New England Journal of Medicine*, the team conducted subsequent genetic tests on over 1,300 individuals with PBC and 1,800 non-PBC patients to identify potential risk loci, or genetic areas of disease susceptibility. Specifically, findings show that genetic risk or 'hot spots' for PBC are genes located in an area that is also involved in the development of systemic lupus erythmatosus, systemic sclerosis and Sjögrens syndrome. Similarly, a second region of interest also shows increased risk and is associated with asthma, Crohn's disease and type 1 diabetes.

"Importantly, our studies have helped to identify three new genetic risk locations, including MMEL1, which has been associated with risk for rheumatoid arthritis and celiac disease," explains Dr. Siminovitch. "We have provided important new evidence that demonstrates there are several shared autoimmune susceptibility loci that contribute to the frequent appearance of additional autoimmune diseases."

Hirschfield GM, Liu X, Han Y, Gorlov IP, Lu Y, Xu C, Lu Y, Chen W, Juran BD, Coltescu C, Mason AL, Milkiewicz P, Myers RP, Odin JA, Luketic VA, Speiciene D, Vincent C, Levy C, Gregersen PK, Zhang J, Heathcote EJ, Lazaridis KN, Amos CI, Siminovitch KA. Nat Genet. 2010 Aug;42(8):655-7. Epub 2010 Jul 18. [Pubmed abstract]. *Research supported by the Canadian Institutes of Health Research, the Ontario Research Fund, the Canadian Primary Biliary Cirrhosis Society, the Canadian Foundation for Innovation, the Ben and Hilda Katz Charitable Foundation, the US National Institutes of Health, the American Gastroenterological Association, and the A.J. and Sigismunda Palumbo Charitable Trust.*

Leukemia: Timing DNA Repair and Cell Death to Prevent Cancer

TGRI Researcher Lauded

UHN congratulates Dr. Richard Weisel for being awarded the American Association for Thoracic Surgery (AATS) Scientific Achievement Award as an individual who has made extraordinary scientific contributions in the field of thoracic surgery. It is the highest Award the AATS can bestow on a member.

Dr. Weisel's research interests have been in the fields of myocardial protection and stem cell therapy. He is being recognized by the AATS for his combination of basic experimental and clinical investigations in the intensive care unit, which has resulted in a new measure of heart function, as well as for having elucidating the molecular events of myocardial ischemia-reperfusion injury.

Congratulations Dr. Weisel!

Did you know?

$22M of UHN's research funding comes from clinical studies? For more information and interesting facts on UHN Research, read the 2009 Research Report.

Hematopoietic stem cells (HSCs) are responsible for life-long blood production and the strategies these cells use to protect against DNA damage are critical to understand in order to learn how the body prevents the development of leukemia (cancer of the blood). Findings from UHN's Dr. John Dick are providing new insights into how human HSCs respond to DNA damage. These findings further deepen our understanding of the mechanisms HSCs employ to regenerate billions of new blood cells without promoting cancer development. This knowledge is important in designing new approaches to harness HSC for stem cell transplantation to cure human diseases.

"We've found some very important data explaining how DNA damage and cell death is regulated in HSCs and, specifically, how p53 and Bcl-2 proteins and regulators of apoptosis, or coordinated cell death, are involved in the process of DNA repair," says Dr. Dick.

The team used HSC isolated from cord blood and exposed them to clinically relevant levels of radiation, which induces DNA strand breaks (DNA damage). When the team examined the timing required for repair, they found that HSCs delay DNA break rejoining and call the DNA damage response (DDR) network into action to assist with repair or to trigger cell death. As a result HSC are more sensitive to radiation compared to other cells already further along the process of developing into a mature cell.

"This study has shown that the DDR of human HSCs differs in many ways from more mature blood cell populations, and p53 and Bcl-2 function in different ways to help prevent cancer cell development," explains Dr. Dick. "Young HSCs take longer to repair and p53 helps balance genome stability and cell death following radiation—a delay that could signify that there are specific mechanisms preventing damaged HSCs from further developing. Moreover, these findings underscore the difference of tumour suppression mechanisms between mice and humans, which is an important consideration in the development of new treatments. Future studies will focus on how the new knowledge regarding the action of p53 and Bcl-2 proteins in human HSC could be employed for therapeutic manipulation."

Milyavsky M, Gan OI, Trottier M, Komosa M, Tabach O, Notta F, Lechman E, Hermans KG, Eppert K, Konovalova Z, Ornatsky O, Domany E, Meyn MS, Dick JE. Cell Stem Cell. 2010 Aug 6;7(2):186-97. Epub 2010 Jul 8. [Pubmed abstract]. *Research supported by postdoctoral fellowships from the European Molecular Biology Organization, the European Hematology Association and the Canadian Institutes for Health Research and The Netherland Society for Scientific Research and grants from The Stem Cell Network of National Centers of Excellence, Canadian Cancer Society Research Institute, Terry Fox Foundation, Genome Canada through the Ontario Genomics Institute, the Ontario Institute for Cancer Research, the Premier's Summit Award through the Ministry of Research and Innovation, the Leukemia and Lymphoma Society, the Canadian Institutes for Health Research, the Canada Research Chairs Program and, in part, by the Ontario Ministry of Health and Long Term Care.*

Alzheimer's Disease: Investigating New Stimulating Treatment Techniques

TWRI's Drs. Andres Lozano, David Tang-Way, Mary Pat McAndrews, John Wherrett and Gary Naglie with PhD student Adrian Laxton have completed the first multi-patient phase I trial investigating the effects of using deep brain stimulation (DBS) for patients with mild Alzheimer's disease (AD). To date, DBS has been investigated as a therapeutic treatment option for patients with depression and Parkinson's disease (PD); however, its effects

on AD have remained unknown.

Explains study lead Dr. Lozano, "We've found evidence showing how DBS to a region of the brain known as the fornix, which is a major inflow and output pathway from the hippocampus and medial temporal lobe that is essential to memory, may improve and/or slow the rate of cognitive decline."

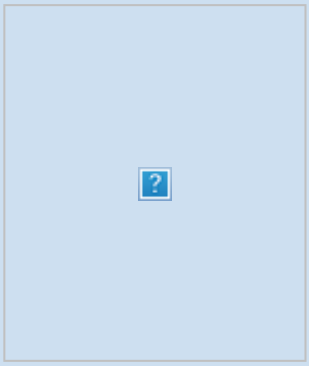
Using state-of-the-art imaging, the team determined that DBS drove neural activity in the memory circuit and reversed impaired glucose (sugar) metabolism in areas that were dysfunctional and accumulate plaques—one of the defining characteristics of damage in AD—early on, effects that were maintained up to a year after the study. It is important to note the impaired glucose metabolism indicates major malfunction in brain areas working in concert to serve memory and cognition and that DBS has a strong effect in reversing this abnormality.

"DBS offers the possibility of modulating brain circuits in an adjustable and reversible fashion, and it appears that this approach can be safe," says Dr. Lozano. "These safety and biological effects are sufficiently compelling to warrant a phase II clinical trial to better understand if DBS may be a potential therapeutic option for patients with AD."

Laxton AW, Tang-Wai DF, McAndrews MP, Zumsteg D, Wennberg R, Keren R, Wherrett J, Naglie G, Hamani C, Smith GS, Lozano AM. Ann Neurol. 2010 Aug 4. [Epub ahead of print]. [Pubmed abstract]. *Research supported by the Neurosurgical Research and Education Foundation, the Dana Foundation, and the Krembil Neuroscience Discovery Fund.*

Neurology: Understanding How Perception of Pain Affects Recovery

Thanks to recent findings from Dr. Karen Davis and colleagues at TWRI, research teams now have a better understanding of how psychological factors and chronic pain are related in patients who have had surgery to repair severed nerves in their upper limbs, more formally known as upper limb peripheral nerve transection and surgical repair (PNIr).



Dr. Davis explains that regardless of whether a patient experiences pain or not following their surgery, they all have problems with their sense of touch, ability to detect warmth, fine dexterity and have impairments in nerve conduction. Importantly, what these study findings are now suggesting, is that there is a relationship between fear and anxiety of movement and the development, intensity and maintenance of chronic pain.

With Dr. Dimitri Anastakis and graduate student Keri Taylor, the team enrolled over 30 patients with PNIr who completed questionnaires to assess psychological factors such as pain characteristics, pain catastrophizing, neuroticism and extraversion, and then underwent sensorimotor evaluation. Findings show that chronic neuropathic pain following PNIr is associated with impaired nerve regeneration, profound sensorimotor deficits and a different psychological profile that may be predictive of poor recovery after injury.

Specifically for patients who experience pain following surgery, chronic pain and augmented sensorimotor deficits may be directly related to incomplete nerve regeneration. Moreover, psychological factors may also contribute to

sensorimotor deficits and chronic pain—neuroticism and catastrophizing may promote fear of movement, avoidance and disuse, and ultimately lead to increased disability. Understanding the psychological factors could help inform health care teams to a patient's potential for the development of pain and increased disability, and provide an avenue for those patients who may require modified therapy treatment plans that include pain coping strategies.

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Taylor KS, Anastakis DJ, Davis KD. Pain. 2010 Jul 22. [Epub ahead of print]. [Pubmed abstract]. *Research supported by the Physicians' Services incorporated and a joint seed grant from the University of Toronto Centre for the Study of Pain/AstraZeneca.*